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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,552	01/18/2002	Ronaldo Alves Pinto Nagem	LUD-5722 US	4555

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FULBRIGHT & JAWORSKI, LLP
666 FIFTH AVE
NEW YORK, NY 10103-3198

EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,552	NAGEM ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-5,8,10,16-22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7,9,11-15 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/2/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group II, claims 6-24, wherein the mutation of amino acid 61 is the elected species reading on claims 6, 7, 9, 11-15 and 23 in the reply filed on June 17, 2004 is acknowledged. Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group I, there is being no allowable generic or linking claim.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Specifically, the specification does not identify IL-22 with a sequence identification number at each occurrence; see for example page 4, second paragraph; page 40, first sentence of the first paragraph; and the legend to Tables 4 and 5.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

35 U.S.C. 101 reads as follows:
Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6, 7, 9, 11-15, and 23 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The specification teaches the three-dimension structure of human IL-22 of SEQ ID NO: 2 determined by X-ray structure. Although the protein is a monomer under physiological conditions and binds to its receptor as a monomer (Logsdon *et al.* and Nagem *et al.*), the crystal structure appears as a dimer. The claims in the instant application are directed to mutants of IL-22 in which the mutation of one or more amino acid residues, presumably, stabilizes the dimer formation in biological fluids, or has a higher affinity to IL-22 receptors. The specification does not report a single mutant of any kind. It is silent on the biological activity of said mutants, which form stable mutants in solution or have higher affinities for IL-22 receptors. The specification does not assert a specific or substantial utility for the dimeric form of IL-2 and mutants with higher affinity for IL-22 receptors, and their use.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 7, 9, 11-15, and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6, 7, 9, 11-15, and 23 are directed to various mutants of IL-22 comprising a mutation at one or more cited positions of any IL-22 protein. The specification does not provide a single representative species of these mutants having any desired characteristics. The specification discloses the three dimensional structure of IL-22, presumably, the human IL-22 of SEQ ID NO: 2 determined by X-ray crystallography. The reported crystal structure is that of an apparent homodimer, whereas IL-22 in solution is a monmer and binds its receptor as a monomer, see page 5, second paragraph, and Logsdon *et al.* [J. Interf. & Cytokine (2002), 22 (11), 1099-1112]. The apparent dimeric structure could be caused by crystal packing and, probably, have no biological significance under physiological conditions. The specification provides substantial speculation about the region(s) in the molecule that interacts with one of two known receptors, but lacks any substantial experimental evidence to corroborate this speculation. Clearly, the specification fails to describe a designed mutant with a stabilized dimer in solution having any function, monomer with enhanced binding to a receptor, or that is useful in the treatment of any disease.

Claims 6, 7, 9, 11-15, and 23 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is not enabling for any mutant at any position which would stabilize the dimeric form of IL-22 or has higher affinity for IL-22 receptor. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to the large number of the claimed mutants, which have a dimeric structure, presumably, in solution, or has higher affinity for IL-22 receptor. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a mutant of IL-22 in which single or multiple mutations is made to stabilize the dimer form of IL-22. The specification provides guidance and examples in the form of an assay to crystallize, presumably, the IL-22 of SEQ ID NO: 2, determine the three dimension structure by X-ray diffraction method, and construct a 3-D model of IL-2, see examples. While

molecular biological techniques and genetic manipulation to make any mutant of IL-22 are known in the prior art and the skill of the artisan are well developed, knowledge regarding stabilizing dimer formation in solution or having a desired pharmaceutical properties or mutants with enhanced binding ability to one or both receptor is lacking. Thus, searching for a mutant with enhanced dimer stability in solution or useful for treating a particular disease is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to such a mutant is enormous. Since routine experimentation in the art does not include determining the three dimensional structure of IL-22 complex with its receptor to identify the binding site(s) in the IL-22 molecule, or screening vast numbers of mutants where the expectation of obtaining the desired IL-22 mutant is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding a method of designing a dimer form of IL-22, the amino acid residues which are involved in binding the receptors, its biological or biochemical activity, and a possible use of said stabilized dimer. It should be noted that the specification provided substantial amount of speculation regarding the binding site(s), which named R1 and R2 without providing any experimental evidence for the actual role of R1 and R2 regions. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 6, 7, 9, 11-15, and 23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) Claims 6, 7, 9, 11-15, and 23 contain the undefined abbreviations "IL-22". Abbreviations and acronyms must be defined at least once in the claims.

(b) The phrases "region 1 or region 2" in claim 6; and "dimerization interface" in claim 11 render the claims indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The specification does not identify the amino acid residues of regions 1 and 2 or those involve in dimer formation, and one of ordinary skill in the art would not know what they are.

(c) The phrases "stabilizing a dimer of IL-22" in claim renders the claim indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase is considered indefinite because it is a relative term and it is not clear relative to what it is being stabilized and in what medium; and how this stabilization will

manifest itself on the equilibrium between the monomer form and the dimer form. Clearly, the wild type IL-22 appears to be stable in the crystal form but not in solution or the gas phase. For examination purposes only, the phrase is disregarded.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 6, 11, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Dumoutier *et al.* [J. Immunol. (2000)Vol. 164, pages 1814-1819]

Dumoutier *et al.* teach the cloning of two protein related to IL-10 induced by IL-9 in mouse T cells and reported their amino acid sequences in Figure 1, see the abstract. The two sequences identified in Figure 1 as mIL-TIFα and mIL-TIFβ are 179 amino acid residues and differ only in two amino acids. The amino acid sequences shown in Figure 1 are IL-22 from mouse. They are highly homologues to the human IL-22 of SEQ ID NO: 2 (~75%) of the instant application, and therefore are considered mutants or variants of SEQ ID NO: 2. The word "comprises" in 6, 11, 14, and 15 indicates that the mutants could contain other mutations. Residues 41, 43, 44, 53, 81, 85, 86, 87, 88, and 179 are different amino acid residues in the mouse proteins shown in Figure 1 from those of SEQ ID NO: 2 (claims 6, 11, 14 and 15).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 11, 14 and 15 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U. S. Patent 6,359,117 ('117).

The '117 patent teaches the amino acid of SEQ ID NO: 27, which is IL-22 from mouse. It is highly homologues to the human IL-22 of SEQ ID NO: 2 of the instant application, and therefore is considered a mutant or a variant of SEQ ID NO: 2. The word "comprises" in 6, 11, 14, and 15 indicates that the mutants could contain other mutations. Residues 41, 43, 44, 53, 81, 85, 86, 87, 88, and 179 are different amino acid residues in the mouse protein of SEQ ID NO: 27 from those of SEQ ID NO: 2 (claims 6, 11, 14 and 15).

These rejections are being made under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 because it is not possible for the Examiner to physically compare the claimed mutant IL-22 and that reported in '117 patent. Applicant bears the burden of providing evidence, which distinguishes the claimed mutant IL-22 from that disclosed in the '117 patent. A preferred means of providing this evidence is for applicant to submit a side-by-side comparison between the polypeptide of SEQ ID NO: 27 of the prior art and the claimed mutants which demonstrates any material differences and shows the claimed mutants to be distinct and unobvious in view of the enzymes of the prior art. *In re Best, Bolton, and Shaw* 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald, Sanders and Bagheri* 205 USPQ 594 (CCPA 1980).

The applied reference has at least a common one inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

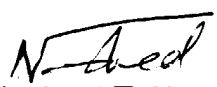
Claims 6, 11, 14, and 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,359,117 ('117). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are claiming the same subject matter. Claims 1 and 2 of the '117 are directed to IL-22 of SEQ ID NO: 27 from mouse. The mouse polypeptide of SEQ ID NO: 27 is 79.5% homologues to the human IL-22 of SEQ ID NO: 2, and therefore considered a mutant. The claimed mutants of the instant application are not limited to specific mutants of SEQ ID NO: 2. The word "comprises" in 6, 11, 14, and 15 indicates that the mutants could contain other mutations. Residues 41, 43, 44, 53, 81, 85, 86, 87, 88, and 179 are different amino acid residues in the mouse protein of SEQ ID NO: 27 from those of SEQ ID NO: 2.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1652